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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/611,835	07/07/2000	Brent R. Stockwell	50164/002002	6924

7590 03/27/2002

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EXAMINER	
FRIEND, TOMAS H F	
ART UNIT	PAPER NUMBER
1627	10

DATE MAILED: 03/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

file copy

Office Action Summary	Application N .	Applicant(s)	
	09/611,835	STOCKWELL ET AL.	
	Examiner	Art Unit	
	Tomas Friend	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-12,14-16,18,20-24,28-33,35,37-44,48,49 and 51-88* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-12,14-16,18,20-24,28-33,35,37-44,48,49 and 51-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Detailed Action

Change of Examiner

The examiner of this application has changed from Barba Koroma to Tomas Friend (formerly Thomas Prasthofer).

Status of the Application

Receipt is acknowledged of a response to an office action with amendment on 28 November 2001 (Paper No. 8).

Status of the Claims

Claims 1-63 were pending. Claims 3, 4, 13, 17, 19, 25-27, 34, 36, 45-47, 50, and 52 were cancelled and new claims 64-88 were added as per applicants' request in Paper No. 8. Claims 1, 2, 5-12, 14-16, 18, 20-24, 28-33, 35, 37-44, 48, 49, 51, and 53-88 are pending in the present application.

Withdrawn Rejections

1. All outstanding rejections are withdrawn.

Objections to the Specification

2. The disclosure is objected to because it contains several embedded hyperlinks and/or other form of browser-executable codes. Applicant is required to delete the embedded hyperlinks and/or other form of browser-executable codes. See MPEP § 608.01.

3. The use of several trademarks including fluo-3, Hydra, and Ivek Digispense 2000, for example, have been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology. Applicants are asked to locate all trademarks in the disclosure and make the appropriate corrections.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claims Rejections – 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 2, 5-12, 14-16, 18, 20-24, 28-33, 35, 37-44, 48, 49, 51, and 53-88 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed methods of screening two-compound or higher combinations for biological activity encompass any assay, any cell type, any biological activity, and any combination of any compounds or class of compounds. Consequently, applicants must show possession of representative examples that would indicate to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of methods that are representative of: [1] any assay, [2] any cell type, [3] any biological activity, and [4] any combination of any compounds or class of compounds. Simply providing exhaustive lists of potential compound classes based upon structure and/or function is not the same as demonstrating that applicants are in possession of methods that use any compounds. Similarly, simply listing numerous assay methods, cell types, and biological activities is not the same as demonstrating that applicants are in possession of methods that use any assay and any cell type to detect any biological activity.

Successfully screening for any synergistic (combination) biological activity using an array of any compounds, any cell type (including prokaryotic, plant, fungus, mammalian, reptilian, insect, etc.), and any assay without guidance as to the compounds to screens, assays to use, or biological activities screened for is unpredictable. Consequently, the importance of representative samples to demonstrate possession of the full scope of the claimed invention is high.

Applicants have exemplified methods which detect an anti-proliferative effect on human A549 lung carcinoma cells using a combinations of 7 FDA-approved drugs and an immunological assay. This example is not representative of the much broader scope of the claimed invention.

5. Claims 1, 2, 5-12, 14-16, 18, 20-24, 28-33, 35, 37-44, 48, 49, 51, and 53-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the assays and test compounds disclosed in the specification, does not reasonably provide enablement for any test compounds and any assay using any cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims without requiring undue experimentation.

Several factors are to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any required experimentation is "undue." These factors include:

1) the breadth of the claims
2) the nature of the invention
3) the state of the prior art
4) the level of one of ordinary skill
5) the level of predictability in the art
6) the amount of direction provided by the inventor
7) the existence of working examples
8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims encompass any compound including, but not limited to, nucleotides and nucleic acids, amino acids and peptides, lipids, glycolipids, sterols, prostaglandins, leukotrienes, proteins, glycoproteins, proteoglycans, glucosaminoglycans, coenzymes, glycerophospholipids, saccharides, polysaccharides, aminoglycosides, peptidomimetics, and fatty acids.

The invention is a method that involves screening combinations of compounds for unexpected results (e.g. synergistic action of two compounds not expected to produce a synergistic action).

Screening of particular classes of compounds for specific biological functions was known in the art. The prior art provides large numbers of cell-based assays for large variety of functional screens for many classes of compounds. Assays were performed on individual compounds or groups of structurally or functionally related compounds that one of ordinary skill in the art would suspect to be active in the screening assay. The compounds screened were not "random" in the sense that there would be no reason to expect them to show activity in the assay being used.

The level of predictability in the art for screening depended on the quality and amount of information used to select test compounds for a particular screen. Screening combinations of compounds that were known to show activity in an assay for synergistic effects was predictable. Many synergistic drug combinations were known in the art. The predictability of screening compounds randomly (i.e. without any structural or functional basis to predict activity in an assay) for synergy was very low. A result showing cooperativity (or synergy) between any two compounds in a cell-based assay without any prior data on structural-function relationships would have been considered "unexpected."

The inventors provide general guidance with respect to a strategy for screening large numbers of compounds for synergistic activity as well as a specific example in which the invention has been reduced to practice. Guidance is lacking, however, with respect to the selection of compounds to be tested for any particular assay. The success of the method would appear to depend upon the ability of one using the invention to select compounds that would include combinations that display synergistic activity. The ability to screen even very large numbers of unnamed compounds (i.e. randomly selected compounds) for an unspecified activity does not overcome the lack of guidance with respect to compound selection for a specific assay.

One of ordinary skill in the art using the claimed method would be "fishing" for an undisclosed activity displayed by a combination of compounds using an unspecified assay. Because no relationship between compounds to be screened or between compounds to be screened and the activity screened for is provided, one of ordinary skill in the art would be required to conduct research to determine the required relationships needed to increase the likelihood of positive results or to rely on searching enormous numbers of compounds without any reasonable expectation that a positive result would be achieved.

Claims Rejections – 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 2, 11, 15, 24, 28, 29, 41, 48, 56, 60-62, and 64-83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 1 requires a minimum of 7 compounds and a minimum number of 49 combinations. A 7x7 array of seven compounds makes 42 combinations and leaves 7 positions containing single compounds. Clarification of the minimum requirements of both compounds and combinations is requested.

B. In claim 1, method step (f), it is not clear if the "*effect on said property of the test cells that is different from the effect of each compound of the combination by itself*" is a different of magnitude for the same property (e.g. cell growth rate) or if the difference is a qualitative difference in property (e.g. cell growth vs. altered gene expression or morphology).

C. Claims 1, 28, 48, and 60 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: determining the effect of each individual compound on the test cell and method steps to link the claimed "*biological property*" to "*detecting or measuring a property of the test cells.*"

D. In claims 1, 28, 48, and 60, it is not possible to determine the metes and bounds of "*a property of the test cells.*" From the claim language, one may interpret that the "*property*" is somehow linked to or indicative of a biological activity but this is not clear. Alternatively, one may interpret "property" to include, for example, location within the array. Clarification is requested.

E. The term "*microfluidics*" in claim 15 is not defined in the specification in such a way that one of ordinary skill in the art could determine the metes and bounds of the term. Page 10 of the specification includes as a part of the definition "*or unconventional methods*" and provides a non-limiting example. Consequently, one would not be able to determine what applicants interpret as "*unconventional methods*" and consequently, "*microfluidics.*"

F. In claims 24, 41, and 56, it is not clear how the term "*synergistic*" further limits the base claim because the base claim appears to inherently detect effects that are "*synergistic.*" It is also not clear of a single compound of the claimed method can act synergistically with a component common to all array positions (a buffer or other growth media component, for example). Clarification is requested.

G. In claims 1, 2, 11, 28, 29, 48, and 60-62, it is not clear if all of the test cells are of the same type or if they may be different cell types.

H. In claims 64-83, the metes and bounds of "*small molecule*" are not clear. It is not clear, for example, if the term includes inorganic as well as organic molecules or what size (in molecular weight or volume) separates a "*small molecule*" from a molecule that is not a "*small molecule.*"

Claims Rejections – 35 U.S.C. 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 2, 11, 12, 14-16, 18, 20-24, 28-33, 35, 37-43, 48, 49, 51, 52-58, and 60-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koller et al. Blood 86(5):1784-1793.

The Koller et al. reference teaches the determination of optimal growth factor combinations for the expansion of CD34-enriched cells in culture (abstract). At least 7 different combinations of at least 9 different growth factors (compounds, FDA-approved drugs and extracts of natural products) were used to assay for the enrichment of CD34 cells during tissue culture in 24-well plate arrays (page 1785, table 1, column 1, second full paragraph, and column 2). Medium was exchanged at various intervals of 2, 3, or 7 days (page 1787). Fluorescence-activated cell-sorting was used to assay for CD34 cell numbers (page 1786, first column) and ELISA was used to assay for endogenous growth factor production (page 1789). Figures 2 and 3 on pages 1787 and 1788 show that combinations of growth factors elicited different levels of total cell expansion (biological activities) from the growth factors alone or in combination with other growth factors (individual growth factors were already known not to be as effective as combinations).

The Koller et al. reference does not explicitly teach specific minimum numbers of compounds or array sizes, sequential addition of compounds to test cells, the use of robotic systems, repeating steps of array formation and assaying 25 times over a one-week period or 100 times over a 30 day period.

It would have been obvious to one of ordinary skill in the art at the time that the invention was made to vary (increase) the array size and the number of compounds tested as needed to screen for growth factors that would enrich cell cultures for CD34 cells. One would have been motivated to do so because the results using 7 the cited combinations, though providing improvements, did not completely satisfy the need in the art for improved growth media (see discussion). One would have had a reasonable expectation for success because the use of only a limited number of combinations produced positive results and one would reasonably expect that using 100, 200, or 1,000 more combinations, for example, would increase the likelihood of discovering better media combinations. The use of robotics and the specific number of repetitions of various steps would have been well within the abilities of one of ordinary skill in the art to determine as design choices based upon the cells to cultured, the duration of tissue culture, and the availability of compounds for testing, for example.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tomas Friend at telephone number **(703) 308-4548**. The examiner can normally be reached on Monday, Tuesday, Friday, and Saturday 8:00-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat can be reached on (703) 308-2439. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-2742.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist at (703) 308-1235.

DR. JYOTHSNA VENKAT PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Tomas Friend, Ph.D.
18 March 2002